Tetrahedron Letters,Vol.24,No.50,pp 5581-5584,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

SYNTHESIS OF SCILLASCILLIN, A NATURALLY OCCURRING BENZOCYCLOBUTENE

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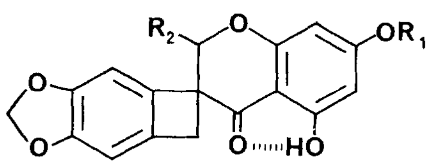
Summary: The novel homoisoflavanone scillascillin has been synthesized from phloroglucinol. The sequence described represents the first synthesis of a naturally occuring benzocyclobutene. The first example of a silyl transfer involving an 8-membered transition state is reported.

Interest in the chemistry of benzocyclobutenes has grown steadily since our first report of the synthesis of the parent hydrocarbon in 1957.[1] Since that time, compounds incorporating the benzocyclobutene system have been studied extensively both from the theoretical point of view and as useful intermediates in natural product total synthesis.[2] In contrast, the only naturally occuring benzocyclobutenes described to date are the novel homoisoflavanones scillascillin (1) and its 2-hydroxy-7-O-methyl derivative (2), both of which have been isolated from the bulbs of Scilla scilloides Druce (Liliaceae).[3] We now report the first synthesis of (±) scillascillin (1).



1: $R_1=R_2=H$
2: $R_1=Me$; $R_2=OH$

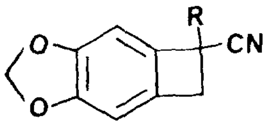
The known 1-cyano-4,5-methylenedioxybenzocyclobutene[4] (3) was treated with LDA in THF at -78°C, followed by gaseous formaldehyde, to give the 1-hydroxymethyl derivative 4 (71%). Attempts to effect a Hoesch condensation[6] of 4 with phloroglucinol (HCl/Et_2O, $ZnCl_2$,0°C) gave a mixture of products from which we could not isolate the desired hydroxy ketone 5. In contrast, nitrile 3 condensed readily with phloroglucinol under similar conditions to give (79%) hydroxy ketone 6, mp 217-219°C.[5] Methylation of 6 (Me_2SO_4, acetone, K_2CO_3) gave (70%)

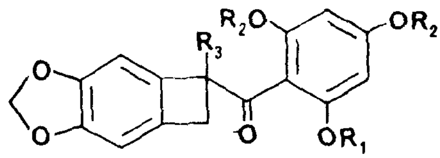
the corresponding trimethyl ether 7.

Various attempts were made to introduce a hydroxymethyl group onto C-1 of the benzocyclobutene ring of either ketone 6 or its trimethyl derivative 7 by reaction with formaldehyde under basic conditions, but these resulted only in polymer formation or recovery of starting material.

Success was achieved with the aid of the t-butyldimethylsilyl protecting group, which does not appear to have been used previously for the blocking of the highly reactive phloroglucinol system.[7] Thus, reaction of ketone 6 with excess t-butyldimethylsilyl chloride [t-$BuMe_2SiCl$(4.0 eq), DMF, imid. 2 days] gave, after flash chromatography, the oily tris(t-butyldimethylsilyl) derivative 8 in 93% yield. An attempted aldol reaction of 8 with paraformaldehyde and a catalytic amount of t-BuOK gave back starting material, but when a full equivalent of base was used a new compound was obtained in good yield (78%). This compound was not the expected alcohol 9 but rather its rearrangement product 10, as evidenced by the hydrogen-bonded phenolic proton at δ 11.6.[5] Evidently the initially formed alkoxide (11) has attacked a neighboring silicon atom to give an intermediate anionic silicon species which has collapsed irreversibly to give a highly stabilized phenoxide ion; in this process a reverse aldolization of alkoxide 11 with the loss of formaldehyde is prevented. Base-catalyzed silyl transfer reactions of diols involving a 5-membered or a 6-membered transition state have been observed previously,[8] but our case is the first reported example involving an 8-membered ring.[9] The three contiguous sp^2 carbons of 11 along with the cyclobutene ring appear to impart sufficient rigidity to the system to facilitate the long-range silyl transfer.

Desilylation of 10 was effected smoothly by 40% aqueous HF in acetonitrile at room temperature.[9] Deprotection of the phenolic groups takes place most rapidly, since the monosilyl derivative 12 can be isolated after 45 minutes; after a reaction time of 2 hours, the tetraol 5 was obtained in quantitative yield. Acid-catalyzed dehydration of the unpurified tetraol 5 [TsOH (cat.), PhH/CH_3CN, 4A sieves, reflux, 2h] afforded (75%) racemic scillascillin (1), mp 210-211.5°C, the spectral properties of which were in accord with those reported for the natural product.[5b]





3: R=H

4: $R=CH_2-OH$

5: $R_1=R_2=H$; $R_3=CH_2OH$

6: $R_1=R_2=R_3=H$

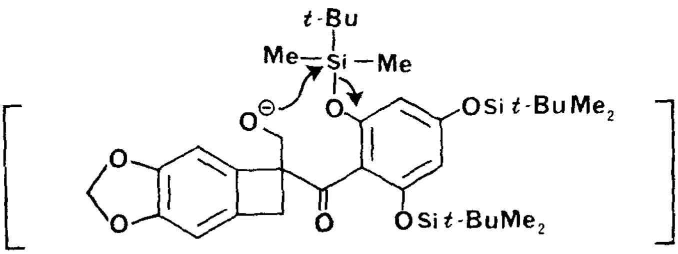
7: $R_1=R_2=Me$; $R_3=H$

8: $R_1=R_2=Si-\underline{t}-BuMe_2$; $R_3=H$

9: $R_1=R_2=Si-\underline{t}-BuMe_2$; $R_3=CH_2OH$

10: $R_1=H$; $R_2=Si-\underline{t}-BuMe_2$; $R_3=CH_2-O-Si-t-BuMe_2$

12: $R_1=R_2=H$; $R_3=CH_2-O-Si-\underline{t}-BuMe_2$



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Acknowledgements. We thank Rohm and Haas for a Graduate Fellowship to V. H. R.

References and Notes

1. M. P. Cava and D. R. Napier, J. Am. Chem. Soc., 79, 1791 (1957).

2. For leading reviews see: a) V. Boekelheide, Acc. Chem. Res., 13, 65 (1980); b) R. L. Funk and K. P. C. Vollhardt, Chem. Soc. Rev., 41 (1980); c) T. Kametani and H. Nemoto, Tetrahedron, 37, 3 (1981); d) I. L. Klundt, Chem. Rev., 70, 471 (1970); e) W. Oppolzer, Synthesis, 793, (1978); f) R. P. Thummel, Acc. Chem. Res., 13, 70 (1980).

3. I. Kouno, T. Komori and T. Kawasaki, Tetrahedron Lett., 4569 (1973); For a review of homoisoflavanones see: W. Heller and C. Tamm., Prog. Chem. Org. Nat. Products 40, 105-152 (1981).

4. Compound 5 has been prepared from 6-bromopiperonal: E. F. Jenny and K. Schenker, Swiss Patent 485,647: CA: 72: P132388d.

5. a)Yields are based on isolation of purified products for which satisfactory spectral data (250 MHz NMR, MS) were obtained.
b) 6 (d_6-DMSO) 3.25-3.4(m, 2H, $-CH_2-$), 5.08-5.11(dd, 1H, J=3.1Hz, 4.9Hz;-C-H), 5.85(s, 2H, Ar-H), 5.89-5.91(d, 2H, J=4.6Hz; $O-CH_2-O$), 6.69(s, 1H, Ar-H), 6.77 (s, 1H, Ar-H), 10.4(br. s, 1H, OH), 12.2(br. S, 2H, OH). 10 ($CDCl_3$) 0.2-0.4(3s, 8H, Si-Me), 0.97-0.98(3s, 27H, Si-t-Bu), 3.26-3.38(dd, 2H, J=15.0Hz, 17.5Hz; $-CH_2-$), 4.0-4.4(2d, 2H, J=11.5H; $-CH_2-OSi$), 5.86(dd, 2H, J=1.2Hz, 5.7Hz; $O-CH_2-O-$), 5.92(d, 1H, J=2.2Hz; Ar-H), 6.00(d, 1H, J=2.1Hz; Ar-H), 6.57(S, 1H, Ar-H), 6.97(s, 1H; Ar-H). 1 (d_6-DMSO) 2.98-3.36(2d, 2H, J=13.5Hz; $-CH_2-$), 4.48-4.63 (2d, 2H, J=11.2Hz, $-CH_2-O$), 5.87-5.91(dd, 2H, J=2.0Hz, 9.0Hz; $O-CH_2-O$), 5.93 (s, 2H, Ar-H), 6.68(s, 1H, Ar-H), 8.29(s, 1H, OH), 12.05(br. s, 1H, OH). HRMS: 312 (M^+, 82), 161(11), 160(100), 159(17.5), 153(60), 112(17), 102(44). Exact Mass: Calcd. for $C_{17}H_{12}O_6$, 312.0634; found, 312.0623.

6. a) R. L. Shriner and C. J. Hull, J. Org. Chem., 10, 288 (1945); b) P. Spoerri and A. DuBois, Org. Reactions, 5, 387 (1949).

7. a) E. J. Corey and A. Venkateswarlu, J. Am. Chem. Soc., 94, 5190 (1972); b) P. M. Kendall, J. V. Johnson and C. E. Cook, J. Org. Chem., 44, 1421 (1979); c) T. W. Green, Protecting Groups in Organic Synthesis, Chapter 3, Wiley, (1981).

8. a) S. S. Jones and C. B. Reese, J. C. S. Perkin I, 2762 (1979); b) Y. Torisawa, M. Shibasaki and S. Ikegami, Tetrahedron Lett., 1865 (1979); c) E. Colvin Silicon in Organic Chemistry, Chapter 15, Butterworths, London (1981).

9. Both tlc and nmr examination of crude 10 showed no evidence of the phenolic phydroxy isomer (R_2=H) of 10, thus ruling out the possibility of intermolecular silyl transfer in this reaction.

10. R. F. Newton, D. P. Reynolds, M. A. W. Finch, D. R. Kelly and S. M. Roberts, Tetrahedron Lett., 3981 (1979).

(Received in USA 9 March 1983)